Blood Pressure Control and Weight Loss in Overweight or Obese Patients with Previously Treated or Untreated Mild to Moderate Hypertension Given Valsartan: An Open-Label Study Comparing Pretreatment and Posttreatment Values

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ABSTRACT

Background: Hypertension is associated with obesity. Recent studies have indicated that therapy with an angiotensin II antagonist, in addition to having an antihypertensive effect, may cause a reduction in body weight.

Objective: The aim of this study was to assess the efficacy and tolerability of valsartan in the treatment of overweight or obese patients with mild to moderate essential hypertension.

Methods: Overweight or obese outpatients aged 18 to ≤ 70 years with previously treated or untreated mild to moderate essential hypertension were eligible for this open-label study conducted at the Department of Internal Medicine and Aging, Clinica Medica II, Policlinico S. Orsola-Malpighi (Bologna, Italy). After a 1-week pharmacologic washout period, patients were treated with valsartan capsules at a fixed dosage of 80 mg once daily for 8 weeks. The dosage was increased to 160 mg once daily if, at 8 weeks, diastolic blood pressure (DBP) was not normalized; otherwise, the 80-mg/d dosage was maintained. Treatment was continued for an additional 16 weeks. Patients' heart rate, systolic blood pressure (SBP) and DBP, body mass index (BMI), and waist-hip ratio (WHR) were measured/calculated at baseline (week 0) and 8, 16, and 24 weeks. Patients were asked to maintain a 1600-kcal/d diet throughout the study.

Results: Forty-eight patients (28 men, 20 women; mean [SD] age, 57 [9] years) were included in the study. In the 45 patients (93.8%) who completed the study, mean SBP, DBP, and BMI were significantly decreased compared with baseline (all $P < 0.001$), but WHR was significantly increased ($P < 0.05$).

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After 24 weeks of treatment, 71.1% of patients had SBP/DBP $\leq 140/\leq 90$ mm Hg. Three patients (6.3%) withdrew from the study due to treatment-related adverse events.

Conclusion: In this population of overweight or obese patients with mild to moderate hypertension, valsartan was well tolerated, and could be effective in controlling blood pressure and achieving weight loss in such patients. (*Curr Ther Res Clin Exp.* 2004;65:172–184) Copyright © 2004 Excerpta Medica, Inc.

Key words: angiotensin II antagonist, mild to moderate hypertension, obesity.

INTRODUCTION

The association between obesity and hypertension has been known for several decades.^{1–4} Hypertension develops in almost 60% of obese individuals compared with 35% of the general population.^{5,6} Moreover, experimental studies^{4,7} have shown that weight gain increases blood pressure (BP) and that weight loss decreases BP in normotensive and hypertensive people, even when sodium intake is held constant.

Although this strong association has been demonstrated, the mechanisms by which obesity causes hypertension are complex and multifactorial. Several abnormalities have been suggested, including volume expansion and cardiac output,^{4,5,7} sodium retention and high sodium intake,^{5,8} enhanced sympathetic nervous system activity,⁵ insulin resistance and hyperinsulinemia,^{5,9} and increased activity of the renin-angiotensin system (RAS).^{10,11}

The RAS has long been recognized as an important regulator of systemic hypertension, and over the past few years local RAS has been detected in various tissues and organs (heart, blood vessels, brain, kidneys, lungs, adrenal glands).^{10,11}

It has been demonstrated in rodent models^{12–15} and in humans^{14–17} that white adipose tissue (WAT) not only is a storage depot of energy substrate, but also, as an endocrine organ, produces and releases numerous peptide hormones and cytokines, including leptin, tumor necrosis factor- α , interleukin-6, and C-reactive protein. It also contains RAS, angiotensin (Ang) II receptors, angiotensinogen (AGT), and enzymes (Ang-converting enzyme [ACE] and non-ACE, tissue chymase, and cathepsin G) required for Ang I conversion to Ang II.^{16,17}

The role of the adipose tissue's RAS in the physiology and pathophysiology of WAT has been established.^{15–17} It has been confirmed that RAS participates in the process of adipogenic differentiation and in the regulation of body weight.^{17,18} Experimental studies^{17,18} have shown that Ang II produced in WAT induces the differentiation of preadipocytes in adipocytes locally through a production loop ("paracrine manner"). Furthermore, a positive correlation

between plasma AGT levels and body mass index (BMI) has been confirmed in different human populations.^{19,20}

Although the involvement of the adipose tissue's RAS in the regulation of body weight has been demonstrated, the role of locally produced Ang II in BP regulation of obese patients remains to be established. In obese, spontaneously hypertensive rats, AGT expression in WAT has been reported to be regulated by food intake.^{21,22} Fasting appeared to be accompanied by a reduction of AGT expression and refeeding by an increase. These local changes in AGT expression were accompanied by parallel changes in BP, which decreased during fasting and increased during refeeding. Therefore, in addition to the explanation of sympathetic hyperactivity, stimulation of adipose tissue AGT expression by food intake may be another possible explanation for the refeeding hypertension model.²³

The complex pathophysiologic background of the hypertensive state associated with obesity has important therapeutic implications because obesity represents a major public health problem in North America and Europe.⁶ In fact, especially in the presence of an increased visceral fat distribution, obesity is a risk factor for cardiovascular disease.^{24,25} It is associated with hypertension, lipid abnormalities, type 2 diabetes mellitus, insulin resistance, and coagulation disorders in individuals with metabolic syndrome (syndrome X).²⁶ Obesity has been reported to be an independent risk factor for the development of coronary atherosclerosis in humans.²⁷ Therefore, reduction of the prevalence of obesity in the population and the protection of obese patients from cardiovascular risks are important medical goals.

An Ang II antagonist, valsartan, was demonstrated to be effective and tolerable in controlling hypertension.^{28,29} The incidence of adverse events (AEs) with valsartan was not significantly greater than with placebo. Compared with ACE inhibitors, the drug was associated with a significantly lower incidence of dry cough because of blockage of the accumulation of bradykinin. Moreover, by directly blocking the Ang II receptors, valsartan avoids the "escape phenomenon" (ie, the increase in plasma Ang II and aldosterone in patients treated with long-term ACE inhibitors).³⁰

This study describes the efficacy and tolerability of valsartan in controlling BP and weight loss in overweight or obese patients with mild to moderate essential hypertension.

PATIENTS AND METHODS

Patients

Overweight or obese ($\text{BMI} \geq 25$ and $< 40 \text{ kg/m}^2$) outpatients aged 18 to ≤ 70 years with previously treated or untreated mild to moderate essential hypertension who met the inclusion (**Table I**) and exclusion (**Table II**)³¹ criteria were considered eligible to participate in the study and were consecutively examined. Written informed consent was obtained from all patients.

Table I. Inclusion criteria.

Age ≥ 18 and ≤ 70 years
Diagnosis of hypertension with diastolic blood pressure ≥ 95 mm Hg and ≤ 115 mm Hg on repeated sphygmomanometry
Body mass index ≥ 25 and < 40 kg/m ²
Waist–hip ratio ≥ 0.81 and < 1.13 (≥ 0.81 for women and ≥ 0.92 for men)
No other medical problems that might affect blood pressure

Study Design and Methods

This 24-week, open-label study was conducted at the Department of Internal Medicine and Aging, Clinica Medica II, Policlinico S. Orsola-Malpighi (Bologna, Italy). The study protocol was approved by the local ethics committee.

The primary investigator performed all measurements and assessments. After a 1-week pharmacologic washout period, all patients began treatment with valsartan capsules at a fixed dosage of 80 mg once daily. Patients who had diastolic BP (DBP) ≤ 90 mm Hg or DBP > 90 mm Hg with a reduction of ≥ 10 mm Hg compared with baseline (week 0) were considered responders. In nonresponders at 8 weeks, the dosage was increased to 160 mg once daily; otherwise, the 80-mg/d dose was maintained. Treatment was continued for an additional 16 weeks.

At baseline, the clinical history of each patient was recorded, and each patient underwent a complete physical examination. Heart rate (HR), systolic BP (SBP), DBP, BMI, and waist–hip ratio (WHR) were measured/calculated at

Table II. Exclusion criteria.

Use of any drug that might lower blood pressure
Pregnant, possibly pregnant, or breastfeeding women
Concomitant use of major psychotropic drugs, steroids, adrenocorticotrophic hormone
Diabetes mellitus, renal insufficiency
Liver dysfunction (alanine aminotransferase and aspartate aminotransferase ≥ 2 -fold normal range and γ -glutamyltransferase ≥ 3 -fold upper limit of normal)
Neoplasm
Bleeding or platelet disorders
Absence of 1 kidney
Alcohol or substance abuse
Mental or legal incapacitation
Secondary form of hypertension ³¹
History of major cardiac arrhythmias
History of heart failure
Previous stroke or transient ischemic attack
Recent (< 6 months) myocardial infarction
Sensitivity, significant adverse reaction, or contraindication to the study drug
Predictable lack of cooperation

baseline (week 0) and at each clinic visit (at 8, 16, and 24 weeks of treatment). BP was measured 24 hours after dosing.

HR was measured over a period of >30 seconds and was assessed after 5 minutes sitting or 2 minutes standing. Immediately after HR measurement, BP was measured 3 times at 1-minute intervals in accordance with the guidelines of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension.³² All 3 BP measurements were recorded in the sitting and standing positions for that visit, and the mean of the measurements was calculated. BP was measured in the arm with the highest BP values, and during follow-up BP was measured in the same arm.

BMI was measured in terms of body weight (kg)/height (m²) ratio; height and body weight were determined without outer clothing or shoes.³³ In this study we used BMI instead of body weight because it is an accurate anthropometric index of adipose tissue changes. It has the advantage of simplicity and is useful for assessing changes in body weight because it correlates better with changes in adipose mass. The patients were classified as overweight or obese in accordance with the American Heart Association criteria.²⁴ Fat distribution was assessed by measuring WHR, with minimal waist and maximal hip girth being measured in the standing position. The cutoff value of the WHR was ≥ 0.81 for women and ≥ 0.92 for men, with the upper limit being <1.13 in both men and women.³⁴

Patients were monitored throughout the study (at 8, 16, and 24 weeks of active treatment) to assess treatment-related clinical and laboratory AEs. Laboratory specimens were taken (for hematology, blood chemistry, and urinalysis) and 12-lead electrocardiography (ECG) and chest radiography were carried out at both study entry and the end of treatment.

It was recommended that patients' dietary intake not exceed 1600 kcal/d. Although no restrictions were placed on the types of foods eaten, patients were told that they would be assessed for body weight loss as well as BP control. Caloric intake was assessed using patient interview. The patients were instructed to measure their body weight monthly at home. Weight also was recorded by the physician at 8, 16, and 24 weeks.

Statistical Analysis

Two subsets of analyses of the primary outcome measures (changes in BP, HR, BMI, and WHR) were performed, one according to the intent-to-treat method and the other using the subgroup of patients who completed the study.

Repeated-measurement analysis of variance was used to analyze the time course of the data. Paired and unpaired 2-tailed *t* tests were used when appropriate. The primary outcome measures were simultaneously tested. For this reason, the limit of significance was reduced in accordance with the Duncan multiple range test.³⁵ The final critical value of significance was therefore set at 0.025.

RESULTS

Forty-eight outpatients (28 men, 20 women; mean [SD] age, 57 [9] years [range, 36–70 years]) were included in the study. Before study entry, 15 patients (31.3%) had been taking an ACE inhibitor; 8 (16.7%), an ACE inhibitor plus a diuretic; and 3 (6.3%), a diuretic only (**Table III**). Seven patients (14.6%) were being treated with a lipid-lowering drug and aspirin for concomitant ischemic heart disease and hypercholesterolemia.

No significant changes were found in HR from baseline to study end.

The mean (SD) SBP of the 45 patients (93.8%) who completed the study was 161 (15.2) mm Hg at baseline and 137 (12.7) mm Hg at the final visit (reduction, 24 [12.7] mm Hg; $P < 0.001$), and the mean (SD) DBP was 103 (7.3) mm Hg at baseline and 84 (8.1) mm Hg at the final visit (reduction, 19 [8.1] mm Hg; $P < 0.001$) (**Table IV**). The BP reductions also were statistically significant at weeks 8 and 16 versus baseline (all $P < 0.001$). Clinically and statistically significant reductions in SBP and DBP (19.5 [14.3] and 13.4 [7.7] mm Hg, respectively) were seen as early as week 8 (both $P < 0.001$).

As the study progressed, a dose adjustment was required for a subset of patients. Table IV reflects changes in the treatment regimen during the course of the study. The BP-reducing effect of valsartan was maintained for the duration of follow-up in patients whose dose was adjusted. By the final visit, patients had experienced mean (SD) reductions of 24 (12.7) mm Hg and 19 (8.1) mm Hg in sitting SBP and DBP, respectively. At the final visit, 32 of 45 patients (71.1%) had DBP ≤ 90 mm Hg and 3 (6.7%) had DBP > 90 mm Hg with a reduction of ≥ 10 mm Hg with respect to the baseline values, giving an overall responder rate of 78.0%. Overall, 32 of 45 (71.1%) patients had BP values $\leq 140/\leq 90$ mm Hg at the final visit.

The mean (SD) BMI values of the 45 patients who completed the follow-up were 33 (4.7) kg/m² at baseline and 31 (4.8) kg/m² at the final visit (reduction, 2 [1.3] kg/m² [5%] [or ~ 4.1 kg of body weight]; $P < 0.001$) without dietary regimen (ie, although it was recommended that patients eat ≤ 1600 kcal, no restrictions were placed on the types of food they ate). Only 11 of 45 patients (24.4%) followed the suggestion of a calorie-restricted diet. In men the mean (SD) BMI was 32.1 (3.8) kg/m² at baseline and 30.3 (3.8) kg/m² at the final visit (reduction, 1.8 [1.5] kg/m²; $P < 0.001$), and in women the mean (SD) BMI was 33.7 [5.8] kg/m² at baseline and 32.3 [5.9] kg/m² at the final visit (reduction, 1.3 [1.0] kg/m²; $P = \text{NS}$). Clinically significant reductions ($P < 0.001$) in BMI were obtained in 35 (77.8%) patients. The BMI reduction from baseline also was statistically significant at 8 and 16 weeks (both $P < 0.001$).

The mean (SD) WHR values of the 45 patients who completed the follow-up were 0.97 (0.07) at baseline and 0.99 (0.09) at the final visit ($P < 0.05$) (1.00 [0.06] for men and 0.93 [0.07] for women at baseline and 1.02 [0.07] for men and 0.94 [0.09] for women at the final visit; $P < 0.05$ and $P = \text{NS}$, respectively).

After 24 weeks of treatment, the men had experienced a higher reduction in BMI than women (5.6% vs 4.1%). In both sexes, the lipolytic effect was observed

Table III. Baseline demographic and clinical characteristics of study patients (N = 48). (Values are expressed as mean [SD] unless otherwise noted.)

Characteristic	Normal Value	Value
Age, y	–	
Mean (SD)		57 (9)
Range		36–70
Sex, no. (%)	–	
Men		28 (58.3)
Women		20 (41.7)
Duration of hypertension, no. (%) of patients	–	
<1 y		12 (25.0)
1–5 y		28 (58.3)
>5–10 y		8 (16.7)
Previous treatment, no. (%) of patients	–	
ACE inhibitor		15 (31.3)
ACE inhibitor + diuretic		8 (16.7)
Diuretic		3 (6.3)
None		22 (45.8)
CAD, no. (%) of patients		7 (14.6)
HR, bpm	70	74 (13)
SBP, mm Hg	≤140	161 (15.0)
DBP, mm Hg	≤90	103 (7.1)
Body weight, kg		
All patients		92 (15.3)
Men		96 (15.4)
Women		86 (13.2)
BMI, kg/m ²	≤25	33 (4.6)
WHR		
All patients		0.97 (0.08)
Men	≥0.92	1.00 (0.07)
Women	≥0.81	0.93 (0.07)
TC, mg/dL	<200	204 (40.9)
HDL-C, mg/dL	Men, 35–65; women, 45–80	47 (10.4)
TG, mg/dL	74–172	137 (75.3)
FBG, mg/dL	60–110	98 (10.0)
Serum uric acid, mg/dL	2.4–7.0	5.4 (1.4)

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; WHR = waist-hip ratio; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; FBG = fasting blood glucose.

more in femoral than in abdominal visceral WAT. Three patients (6.3%) did not complete the study because of clinical AEs, but were followed up for 24 weeks. BP was controlled by a diuretic and calcium channel blockers, but no significant modification in weight was observed. None of the AEs these patients experienced were considered serious. The most frequently reported AEs were

Table IV. Mean (SD) changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist–hip ratio (WHR) in the patients who completed the study (N = 45).

Parameter	Normal Value	Study Week			
		0	8	16	24
HR, bpm	70	74 (13)	73 (11)	75 (12)	73 (11)
SBP, mm Hg	≤140	161 (15.2)	141 (14.3)*	139 (13.7)*	137 (12.7)*
DBP, mm Hg	≤90	103 (7.3)	90 (7.7)*	86 (7.8)*†	84 (8.1)*‡
BMI, kg/m ²	≤25				
All patients		33 (4.7)	32 (4.8)*	32 (4.9)*	31 (4.8)*‡§
Men		32.1 (3.8)	31 (4.0)	31 (4.0)	30.3 (3.8)*‡
Women		33.7 (5.8)	33 (5.6)	33 (5.9)	32.3 (5.9)§#
WHR					
All patients	≥0.81 and <1.13	0.97 (0.07)	0.97 (0.08)	0.99 (0.08)	0.99 (0.09)†¶
Men	≥0.92	1.00 (0.06)	1.00 (0.07)	1.02 (0.07)¶#	1.02 (0.07)¶#
Women	≥0.81	0.93 (0.07)	0.92 (0.07)	0.93 (0.08)	0.94 (0.09)#

**P* < 0.001 versus baseline.†*P* < 0.005 versus 8 weeks.‡*P* < 0.001 versus 8 weeks.§*P* < 0.005 versus 16 weeks.||*P* < 0.005 versus baseline.¶*P* < 0.05 versus baseline.#*P* < 0.05 versus 8 weeks.

insomnia and headache (1 patient [2.1%]); dizziness, asthenia, and muscular pain (1 patient [2.1%]); and epigastric pain (1 patient [2.1%]). All of these AEs were considered treatment related except muscular pain. No clinically important changes in laboratory safety data were found. More than 90% of the patients came within the predefined limits of change with regard to each of the laboratory parameters assessed. No abnormalities were observed on ECG or chest radiography.

In the intent-to-treat population, a significant reduction of outcome measures was observed only for DBP values at study end (**Table V**). In the 3 patients who withdrew, BP was controlled using calcium channel blockers. No significant changes in body weight were observed in these patients.

DISCUSSION

In the present study, valsartan given at a fixed dosage of 80 or 160 mg once daily for 24 weeks was effective and tolerable in controlling BP in overweight or obese outpatients with previously treated or untreated mild to moderate essential hypertension. Clinically and statistically significant reductions in BP were seen as early as 8 weeks of treatment, suggesting that valsartan is effective

Table V. Mean (SD) changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist-hip ratio (WHR) in the entire intent-to-treat population (N = 48).

Parameter	Normal Value	Study Week			
		0	8	16	24
HR, bpm	70	74 (13)	73 (11)	75 (12)	73 (11)
SBP, mm Hg	≤140	161 (15.0)	142 (14.5)*	139 (13.7)	137 (12.7)
DBP, mm Hg	≤90	103 (7.1)	90 (8.0)*	86 (7.8)*	84 (8.1)*
BMI, kg/m ²	≤25				
All patients		33 (4.6)	32 (4.7)	32 (4.9)	31 (4.8)
Men		32 (3.7)	31 (4.0)	31 (4.0)	30 (3.8)
Women		33 (5.6)	33 (5.4)	33 (5.9)	32 (5.9)
WHR					
All patients	≥0.81 and <1.13	0.97 (0.08)	0.97 (0.08)	0.99 (0.08)	0.99 (0.09)
Men	≥0.92	1.00 (0.07)	1.00 (0.07)	1.02 (0.07)	1.02 (0.07)
Women	≥0.81	0.93 (0.07)	0.92 (0.07)	0.93 (0.08)	0.94 (0.09)

**P* < 0.001 versus baseline.

in the initial treatment of hypertension in overweight or obese, hypertensive patients.

Because this was an open-label study design, comparison with placebo or other medications was not performed. However, controlled trials have shown the antihypertensive efficacy of Ang II antagonist alone and in combination with a low-dose diuretic.^{36,37}

In a meta-analysis, Conlin et al³⁸ assessed 43 published randomized controlled trials with losartan, valsartan, irbesartan, and candesartan alone or in combination with low-dose hydrochlorothiazide (HCTz). Of 11,281 hypertensive patients, responder rates for Ang II antagonist monotherapy ranged from 48% to 55% (absolute weighted average DBP reduction, 8.2–8.9 mm Hg) and antihypertensive efficacy was comparable for all the agents. With the addition of 12.5 mg of HCTz, responder rates increased to a range of 56% to 70% (reduction, 9.9–13.6 mm Hg).

Our data are near those seen in a 12-week, multicenter, double-blind, randomized, parallel-group study of 127 obese adult patients with mild to moderate essential hypertension (Candesartan Role on Obesity and on Sympathetic System study).³⁹ That study assessed the effect of an Ang II antagonist (candesartan cilexetil) compared with a diuretic (HCTz) on hypertension, insulin resistance, and sympathetic activation. After 12 weeks of double-blind treatment, BP was controlled in 86.8% of the patients taking candesartan cilexetil and 78% of those taking HCTz. In addition, the patients treated with an Ang II antagonist showed a significant reduction in insulin resistance, which frequently occurs in obese patients and, because of the positive interaction between Ang II and the

sympathetic nervous system, a reduction in sympathetic activation (another major abnormality of obese individuals) also was seen.

In our study, valsartan, in addition to being effective in controlling BP, was also effective in reducing BMI. Because patients were not restricted in the types of foods they ate, and because only ~25% followed the 1600 kcal/d recommendation, we can speculate that the decrease in BMI was not due entirely to diet and that the decrease in BP was not entirely related to weight loss.

The reduction in body weight we observed after treatment is important because weight loss improves many of the medical complications associated with obesity (eg, hypertension, insulin resistance, hyperlipidemia), and that beneficial effect begins after only modest weight loss of 5% to 10% of initial body weight.⁴⁰

In obese patients, the involvement of Ang II as the result of increased AGT secreted by WAT has been proposed⁴¹ in the development of hypertension associated with obesity. It is hypothesized that along with several other consequences, transient or chronic AGT overexpression in WAT may lead to a cycle in which the development of WAT is further increased by enhanced AGT secretion and Ang II production, at the same time leading to increased BP.^{18,19,41}

This hypothesis was supported by experimental observations in animals¹⁸ and in vitro.^{19,41} Unfortunately, the study in rodents by Ailhaud et al¹⁸ was not reproducible with cultured human preadipocytes, in which Ang II inhibits adipogenic differentiation, whereas its blockade with Ang I receptor antagonist promotes differentiation of the cells.⁴² In any case, the experimental data cannot be definitely related to the results of an open-label, placebo-controlled study in which the absence of the other arm precludes direct estimate of the efficacy of the therapy in terms of SBP, DBP, BMI, and WHR values.

A final point concerns the effect of valsartan on distribution of lipid mass. After 24 weeks of treatment, the men had experienced a higher reduction in BMI than the women (5.6% vs 4.1%). In both, the lipolytic effect was observed more in femoral (subcutaneous) than in abdominal (visceral) WAT. These data seem to conflict with those of experimental studies that demonstrated that the expression of the AGT gene is higher in visceral fat than in subcutaneous fat.⁴³

In humans, lipolytic function in WAT mass is controlled not only by Ang II but also by several hormones: insulin, catecholamines, and natriuretic peptide.⁴⁴ Catecholamines are of great importance for the regulation of lipid mobilization and, in vitro, there are different catecholaminergic controls of fat cells from various fat deposits.⁴⁵ Moreover, Ang II inhibits lipolysis in WAT, and the femoral depot seems to be more sensitive to this effect than the abdominal depot.⁴⁶ The problem is complex and needs to be clarified by further studies.

Although this pilot study was relatively small, most of the expected results were obtained. However, the study does have some additional limitations. It was an open-label study that was not randomized or controlled. The absence of a control arm precluded direct estimates of placebo-adjusted reduction in SBP, DBP, BMI, and WHR values. The study was carried out with a limited number of

patients and over a relatively short period (24 weeks). This short period may not provide an adequate estimate of the long-term efficacy and tolerability of therapy. Another limitation of the study was that a fixed forced-titration dose of valsartan was used.

A forced-titration design was chosen to facilitate a comparison of the recommended once-daily maximum dosage of this drug using the usual titration regimen.

CONCLUSIONS

Our data indicate that blockade of Ang II for 24 weeks with an Ang II antagonist (valsartan 80 or 160 mg once daily) significantly controlled BP and may cause weight loss in overweight or obese patients with previously treated or untreated mild to moderate essential hypertension. If the data of this pilot study are confirmed in a larger and longer, controlled trial, these findings may have implications for the use of this Ang II antagonist in modulating the mechanisms that predispose overweight or obese patients to hypertension and its clinical consequences.

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